REMARKS

Claims 1, 3-11, 13-15, 17, 18 and 20-25 are pending. Claims 4, 5, 7-11, 13-15, 17, 18, 20, 22 and 23 are withdrawn as being drawn to a non-elected invention. Claims 1, 3, 6, 21, 24 and 25 are currently under examination.

Claims 1, 6, 24 and 25 are amended herein. Claim 21 is canceled herein without prejudice. The amendments add no new matter.

Objection to the Drawings:

The Examiner objected to Figure 10 because Figure 10A appears to have been omitted. The Office Action states that Figures 10B-10I should be labelled 10A-10H, respectively, and the Brief Description of the Drawings should be amended accordingly.

Applicants submit herewith an amended Figure 10, showing panels 10A – 10H, including a clean version and a marked-up version showing the amendments. Applicants have also amended the Brief Description of the Drawings as requested. The amendments add no new matter.

Claim Objections:

Claims 21 and 24 are objected to because both claims depend from a non-elected claim.

Applicants have amended claim 24 herein and made it independent. Applicants have canceled claim 21. These modifications are believed to fully address the stated objections.

Double Patenting:

The Office Action states that "should claim 21 be found allowable, claim 24 will be objected to under 37 C.F.R. 1.75 as being a substantial duplicate thereof," and that "claims 21 and 24 cover the identical scope." Applicants' cancellation herein of claim 21 and amendment of claim 24 both render this objection moot.

Rejections under 35 U.S.C. §112:

Written Description:

Claims 1, 3, 6, 21, 24 and 25 are rejected under 35 U.S.C. §112, first paragraph for lack of written description. The Office Action states

> "The chaperone, nucleic acid, or non-protein, non-nucleic acid compound to be administered to a mammal is an essential element of the claimed invention. However, the specification only describes a single species of therapeutic compound, namely HDJ-2/HSDJ, that could be used in the claimed methods. The specification does not describe any compound that could be used in practicing the method of the invention for treatment of Alzheimer's disease, Parkinson's disease, prion diseases, or any other neurodegenerative disease other than SCA-1. In the absence of a written description of the therapeutic compounds, the claimed methods lack written description for the complete genus because the therapeutic compound is an essential element of the claimed method..... In this case, no compounds other than HDJ-2/HSDJ are described...."

Applicants respectfully disagree.

First, Applicants submit that the rejection is moot with respect to claim 21, which is canceled herein.

Second, Applicants submit that, contrary to the assertion in the Office Action, HDJ-2/HSDJ is not the only species of therapeutic compound described. The specification teaches that chaperones are useful for the treatment of neurodegenerative diseases characterized by insoluble aggregates in cells of the nervous system, and describes a number of chaperones in addition to the HDJ-2/HSDJ chaperone molecule. For example, the specification specifically refers to HSP60, HSP40, and HSP70 as examples of chaperone proteins at page 10, lines 10-13, in the definition of "chaperone." Hsp40 is additionally taught to be part of a family of chaperones that includes HDJ-2/HSDJ at page 22, lines 17-21. HSP70 is additionally taught to be part of a family of chaperones at page 22, lines 28-31. Applicants submit that the structures of HDJ-2/HSDJ, HSP40, HSP60 and HSP70 are known in the art, as is their function as chaperones. Thus, the specification describes at least four individual chaperones and, because two of these are specifically taught to be members of families, the specification describes a larger number still.

Next, Applicants submit that the term "chaperone" refers to protein chaperones in the definition, at page 10, lines 6-13, which states in relevant part "the term 'chaperone' refers to those proteins which are produced in eukaryotic cells that either help other proteins to fold or allow misfolded proteins to re-fold into proper structure." Thus, description of protein chaperones is sufficient to satisfy written description.

Further, the Office Action commented on a lack of a description of "any compound that could be used in practicing the method of the invention for treatment of Alzheimer's disease, Parkinson's disease, prion diseases or any other neurodegenerative disease other than SCA1." Applicants submit that the specification teaches that "Alzheimer disease, Parkinson disease, the prion disorders, Huntington disease (HD), dentatorubral-pallidoluysian atrophy (DRPLA), spinocerebellar ataxia-type 1 and 3 (SCA1 and SCA3) and any other disease caused by CAG repeat expansion" are *all* examples of "neurodegenerative disorders that have the characteristic of insoluble aggregates in the cells of the nervous system" (page 10, line 26 to page 11, line 2). In fact, the term "neurodegenerative disorders" is defined in the specification as referring to those neurodegenerative disorders which have the characteristic of insoluble aggregates in the cells of the nervous system (page 10, lines 26 to 29). Thus, a chaperone that modifies the protein aggregation behavior of a protein involved in one of these disorders is a candidate for treatment of that disorder.

With regard to structure of chaperone molecules useful according to the invention, the specification describes the four conserved domains of the HDJ-2/HSDJ protein at page 3, lines 21-34. Specifically, the specification teaches that a zinc-finger-like domain is necessary for folding polypeptides once bound, and that the C-terminal domain binds unfolded polypeptides and has been shown essential for preventing aggregation of a model substrate. Thus, the specification provides description of the conserved structural domains of the exemplified HDJ-2/HSDJ chaperone, and provides a structure/function correlation between the conserved domains and chaperone activity of the HDJ-2/HSDJ protein.

In view of the above, Applicants submit that the specification provides adequate written description of a sufficient number of chaperones to satisfy the written description requirement

under 35 U.S.C. §112, first paragraph. Applicants respectfully request reconsideration and withdrawal of the rejection.

Enablement:

Claims 1, 3, 6, 21, 24 and 25 are rejected under 35 U.S.C. §112, first paragraph for lack of enablement. The Office Action states that "the claims encompass protein therapy, gene therapy, and non-protein, non-nucleic acid compound therapy" and concludes that "thus, the claims are very broad in scope with regard to the type of compound to be administered." The Office Action further states that "the claims are very broad with regard to the type of disease to be treated," that "the claims cover a wide variety of neurodegenerative diseases," and that "the claims are very broad in scope with regard to the type of therapeutic effect to be achieved by the method." The Office Action notes that there are no working examples of the claimed invention. The Office Action concludes that "given the limited examples, the limited guidance in the specification, the lack of any showing of therapeutic benefit upon in vivo administration of a compound as recited in the claims, the broad scope of the claims, and the unpredictability for producing a therapeutic effect upon administration of a compound as recited in the claims, undue experimentation would have been required for one of skill in the art to develop a protocol within the scope of the claims for treating a wide variety of neurodegenerative diseases. Applicants respectfully disagree.

First, with regard to gene therapy, Applicants have amended claims 1, 6 and 25 to recite the introduction or administration of a "chaperone preparation" or "compound preparation." Support for the language of the amendment is found, for example, at page 17, lines 1-30 which describe exemplary preparations for administration of chaperones or compounds as described in the specification. Thus, claim 1 as amended recites "introducing a therapeutic effective amount of a chaperone preparation into the neurological system of the mammal," and claims 6 and 25 as amended recite "introducing a therapeutically effective amount of a compound preparation into said mammal" and "introducing a therapeutically effective amount of a compound preparation which suppresses ataxin-1 aggregation into the neurological system of the mammal," respectively. Applicants submit that the introduction of a compound preparation or a chaperone preparation does not encompass gene therapy approaches, because the cells or vectors introduced

in gene therapy approaches do not constitute a preparation of either the compound or the chaperone. Rather, in gene therapy approaches, the material introduced, i.e., cells or a vector, is a way to *make* the chaperone, not a chaperone or compound preparation itself. Thus, the claims as amended do not encompass gene therapy.

With regard to the assertion that the type of compound or chaperone recited to be administered in the claims is overly broad, Applicants submit that the definition of the term "chaperone" as it is used in the specification refers to "those proteins which are produced in eukaryotic cells that either help other proteins to fold or allow misfolded proteins to re-fold into proper structure" (page 10, lines 6-9). Applicants submit that chaperone proteins are well known in the art. For example, on page 3, the specification refers to: Lu et al., "The conserved carboxyl terminus and zinc finger-like domain of the co-chaperone Ydj1 assist HSP70 in protein folding," Journal of Biological Chemistry 273: 5970-5978 (1998; **Exhibit A**); Hartl, "Molecular chaperones in cellular protein folding," Nature 381: 571-580 (1996; **Exhibit B**); and Hendricks et al., Molecular chaperone functions of heat shock proteins," Ann. Rev. Biochem. 62: 349-384 (1993; **Exhibit C**). As such, Applicants submit that the claims are not overly broad in referring to chaperones.

With regard to the assertion that "the claims encompass a wide variety of neurodegenerative diseases," Applicants submit that, as discussed above, the term "neurodegenerative disorders" is defined in the specification to encompass only those neurodegenerative disorders "which have the characteristic of insoluble aggregates in the cells of the nervous system." The possibility, mentioned in the Office Action, that the different insoluble aggregate-related neurodegenerative diseases, e.g., Alzheimer's disease, Parkinson's disease, the prion disorders, Huntington's disease (HD), dentatorubral-pallidoluysian atrophy (DRPLA), spinocerebellar ataxia-type 1 and 3 (SCA1 and SCA3) and any the other CAG repeat expansion diseases do not have the same "cause" does not overcome the fact that they all do have insoluble aggregate accumulation as a common factor. Applicants submit that the claimed approach, involving the introduction of chaperones, is one shown in the examples, and in post-filing literature references, to reduce neurodegeneration in models of neurodegenerative disease that involve the formation of insoluble aggregates.

Examples of post-filing publications which support the enablement of the claimed invention include the following:

1) Cummings et al., 2001, "Overexpression of inducible HSP70 chaperone suppresses neuropathology and improves motor function in SCA1 mice," Hum. Mol. Genet. 10: 1511-1518. **(Exhibit D)**

This reference reports the results obtained from the double-transgenic animals described in Example 9 of the specification. SCA1 mice (B05 mice, expressing a mutant allele of SCA1 in Purkinje cells) were crossed with mice expressing a human HSP70 gene, and the animals were evaluated at both the behavioral and cellular levels for differences in SCA-1 pathology. The animals that expressed both the mutant SCA-1 allele and the HSP70 chaperone fared significantly better in the behavioral tests than those expressing the SCA-1 allele only. The effect was dependent on the level of the HSP70 chaperone expressed. Similarly, histological analysis showed that Purkinje cell degeneration was reduced in the double transgenics relative to those expressing only the SCA-1 allele. This reference therefore supports the enablement of the claimed invention in that the chaperone HSP70 ameliorated the neurodegenerative pathology in an accepted mammalian model of human neurodegenerative disease.

2) Adachi et al., 2003, "Heat Shock Protein 70 chaperone overexpression ameliorates phenotypes of the Spinal and Bulbar Muscular Atrophy transgenic mouse model by reducing nuclear-localized mutant androgen receptor protein," J. Neurosci. 23: 2203-2211. **(Exhibit E)**

This reference demonstrates that high expression of HSP70 markedly ameliorated the motor function of Spinal and Bulbar Muscular Atrophy (SBMA) model mice. This reference also therefore supports the enablement of the claimed invention in that the chaperone HSP70 ameliorated the neurodegenerative pathology in an accepted mammalian model of human neurodegenerative disease.

3) Bonini, 2002, "Chaperoning brain degeneration," Proc. Natl. Acad. Sci. U.S.A. 99: 16407-16411. **(Exhibit F)**

This reference reviews studies in Drosophila models of human neurodegenerative disease and the role of chaperones in suppressing the disease phenotype. The reference states that:

> "Drosophila has emerged as a premier model system for the study of human neurodegenerative disease. Genes associated with neurodegeneration can be expressed in flies, causing phenotypes remarkably similar to those of the counterpart human diseases."

In addition to results showing suppression of disease phenotype by chaperones HSP70 and HSP40 in a Drosophila model of the Machado-Joseph polyglutamine repeat disease, the reference reports results in a Drosophila model of Parkinson's disease, which is also characterized by abnormal accumulation of protein aggregates termed "Lewy bodies." The directed expression of α-synuclein leads to adult-onset degeneration of dopaminergic neurons in Drosophila, providing a model for Parkinson's disease. The reference teaches that the co-expression of α-synuclein and HSP70 dramatically enhanced the maintenance of dopaminergic neurons in this model.

4) Warrick et al., 1999, "Suppression of polyglutamine-mediated neurodegeneration in Drosophila by the molecular chaperone HSP70," Nature Genetics 23: 425-428. **(Exhibit G)**

This reference demonstrates that neurodegeneration in a Drosophila model of polyglutamine disease is suppressed by the molecular chaperone HSP70. Eye-specific expression of the human Machado-Joseph disease (MJD) protein having a 78 glutamine repeat induces retinal degeneration in this Drosophila model. Co-expression of human HSP70 completely rescued external eye pigmentation and partially restored retinal structure. Further, co-expression of the human HSP70 in all tissues partially restored viability to flies expressing the MJD mutant in all tissues, thereby demonstrating the effectiveness of the HSP70 chaperone in an accepted model of human disease.

5) Carmichael et al., 2000, "Bacterial and yeast chaperones reduce both aggregate formation and cell death in mammalian cell models of Huntington's disease," Proc. Natl. Acad. Sci. U.S.A. 97: 9701-9705. **(Exhibit H)**

This reference teaches that fragments of the bacterial chaperone GroEL and full length yeast chaperone HSP104 reduce both insoluble aggregate formation and cell death in both neuronal (PC-12) and non-neuronal cell culture models of Huntington's disease. The reference validates the applicability of even non-mammalian chaperones for the reduction of cell death,

and, by showing that chaperone-mediated aggregate reduction reduces cell death, further supports the correlation between aggregate formation and cell death.

6) Jana et al., 2000, "Polyglutamine length-dependent interaction of Hsp40 and Hsp70 family chaperones with truncated N-terminal huntingtin: their role in suppression of aggregation and cellular toxicity," Hum. Mol. Genet. 9: 2009-2018. **(Exhibit I)**

This reference shows that the overexpression of HSP40 and HSP70 chaperone family members reduces both insoluble protein aggregation and cell death in mouse neuronal cell lines inducibly expressing a pathogenic polyglutamine expanded form of huntingtin. Thus, chaperones reduce cell death in yet another model of human neurodegenerative disease.

7) Kobayashi et al., 2000, "Chaperones Hsp70 and Hsp40 suppress aggregate formation and apoptosis in cultured neuronal cells expressing truncated androgen receptor protein with expanded polyglutamine tract," J. Biol. Chem. 275: 8772-8778. **(Exhibit J)**

This reference shows that the overexpression of HSP70 and HSP40, separately and in combination in a mouse neuronal cell model (Neuro2a cells) of human SBMA, suppressed insoluble aggregate formation and cell death. This reference also supports the applicability of the results from in vitro cell culture systems to in vivo systems, in that the Adachi et al. reference (#2 above; **Exhibit E**) confirms that the effect of the expression, in transgenic mice, of the same pathological protein reported in this reference can be countered by the same chaperone in the that mouse system.

8) Ishihara et al., 2003, "Hsp105α suppresses the aggregation of truncated androgen receptor with expanded CAG repeats and cell toxicity," J. Biol. Chem. 278: 25143-25150. **(Exhibit K)**

This reference shows that the expression of the human Hsp105α chaperone suppresses the aggregation of truncated androgen receptor with an expanded polyglutamine repeat and suppresses cell death in both COS-7 cells and the neuroblastoma cell line SK-N-SH.

With regard to the assertion that there are no working examples of the claimed invention, Applicants submit that animal model and in vitro model studies are sufficient to provide enablement for methods performed in humans where there is an adequate correlation between the

in vitro or in vivo animal model and a disclosed or claimed method of use. Thus, an in vitro or in vivo animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. Where, the animal or in vitro model is recognized in the art as correlating with a specific condition, e.g., a specific neurodegenerative disease, then it should be accepted as correlating unless the Examiner has evidence that the model does not correlate. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that in vitro data did not support in vivo applications). A rigorous or an invariable exact correlation is not required, as stated in Cross v. Iizuka, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985). In view of this, Applicants submit that the description of in vitro and animal model examples, both in the specification and in subsequent post-filing publications, provides an enabling disclosure for the claimed methods. Specifically: Example 8 in the specification shows that the HDJ-2/HSDJ chaperone reduces ataxin-1 aggregation in vitro; Example 9 and the post-filing reference Cummings et al. (Exhibit D) show that HSP70 reduces the pathology in an accepted mouse model of SCA-1; Adachi et al., 2003, (Exhibit E) shows similar results in an accepted mouse model of SBMA; and Bonini et al., 2002 (Exhibit F) and Warrick et al. (Exhibit G) each show positive results with HSP70 chaperone in accepted Drosophila models of human neurodegenerative diseases including MJD and Parkinson's disease. Finally, the various cell culture models described above are also accepted models that correlate with specific human diseases. As noted, the applicability of the in vitro cell culture data to the claimed methods is strengthened, for example, by the demonstration that the effects of the expression of the same pathologic protein (androgen receptor) in both the cell culture (i.e., Kobayashi et al., Exhibit J, and Ishihara et al., Exhibit K) and transgenic animal model systems (i.e, Adachi et al., Exhibit E) are countered by expression of the same chaperone, HSP70. In view of the correlations between the animal models and the cell culture models and in view of the correlation of each of these models to human disease, Applicants submit that the specification and post-filing literature references in agreement with the teachings in the specification provide proof of enablement for the claimed methods.

Rejection under 35 U.S.C. §102(a):

Claims 1, 3 and 6 are rejected as lacking novelty over WO 97/43649 (Weiss et al., published November 20, 1997). The Office Action states that "Weiss et al. describes the administration of a chaperone, particularly Hsp60, for the treatment of transmissible spongiform encephalopathy (page 9, paragraphs 4 and 5)" and that "although the reference does not disclose specific treatment effect, the instant specification provides no more guidance than the prior art." The Office Action thus concludes that the claimed invention is taught in the prior art. Applicants respectfully disagree.

Applicants submit that the Weiss et al. reference does not anticipate the claimed invention because its teachings with regard to the administration of a chaperone are equivocal, with the authors stating that "*it might possible* to block the conversion of the isoform PrPc into the prion associated form PrPsc by administration of" a chaperone such as Hsp60 ***or*** :

> "On the other hand, it *might be possible* that chaperones are involved in the transformation of PrP^{c} to PrP^{sc}. Thus, blocking such transformation by the administration of agents which specifically inactivate such chaperones which specifically interact with prion proteins could also be helpful for the treatment or prevention of transmissible spongiform encephalopathies."

Thus, the authors provide directly contradicting methods for treatment of the same condition and essentially admit to having no idea of which approach should be used. The discussion is pure speculation.

Applicants submit that a reference, in order to be anticipatory, must be enabling for the material of the claim it is said to anticipate. The reference must be enabling and describe the applicant's claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention. *In re Paulsen*, 30 F. 3d 1475, 1479 (Fed. Cir. 1994); *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990). Given the contradictory nature of the reference's teachings, Applicants submit that the reference is not enabling for a method of treating neurodegenerative disease in a mammal comprising the step of introducing a therapeutic effective amount of a chaperone preparation into the neurological system of the mammal.

In this regard, Applicants respectfully submit that the Office Action's assertion that "although the reference does not disclose the specific treatment effect, the instant specification provides no more guidance than the prior art" is not relevant. Applicants have addressed the Office Action's questions regarding enablement of the instant claims herein above. Further, Applicants submit that the Weiss et al. reference not only fails to provide a "specific treatment effect," but fails to indicate whether one should administer an HSP60 chaperone or an *inhibitor* of the very *same* chaperone to treat the very *same* disease. Given this lack of guidance in the Weiss et al. reference, it would require undue experimentation for one of skill in the art to perform the method said to be taught by Weiss et al. As such, the reference is non-enabling and cannot therefore anticipate the presently claimed invention.

In view of the above, Applicants submit that all issues raised in the Office Action have been addressed herein. Applicants respectfully request reconsideration of the claims.

Respectfully submitted,

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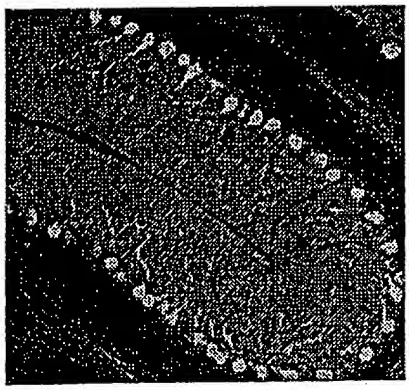

Figure 10A

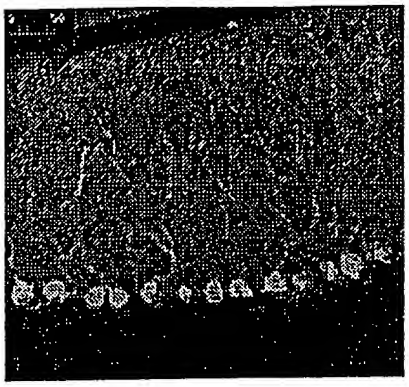

Figure 10B/A

Figure 10C/B

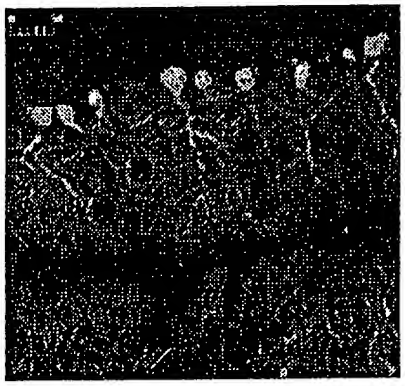

Figure 10D/C

Figure 10E/D

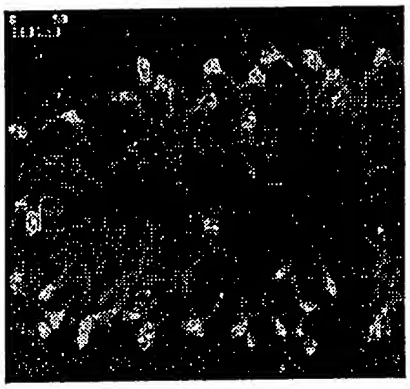

Figure 10F/E

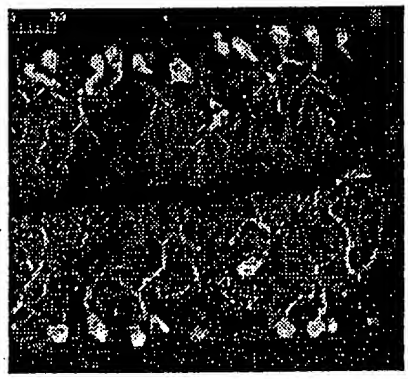

Figure 10G/F

Figure 10H/G

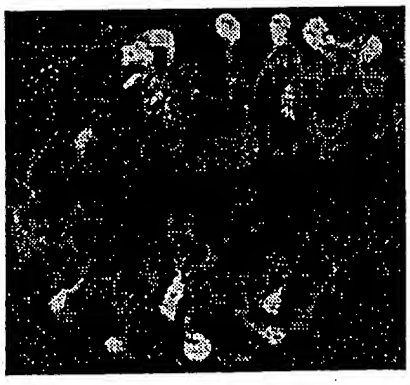

Figure 10I/H